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Irradiation of the Tumor Bed Alone After Lumpectomy in Selected Patients With Early-Stage Breast Cancer Treated With Breast Conserving Therapy

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Backgrounds and Objectives: We present the interim findings of our in-house protocol treating the tumor bed alone after lumpectomy with low-dose-rate (LDR) interstitial brachytherapy in selected patients with early-stage breast cancer treated with breast conserving therapy (BCT).

Methods: From 1 March 1993 through 1 January 1995, 50 women with early-stage breast cancer were entered into a protocol of tumor bed irradiation alone using an interstitial LDR implant. Patients were eligible if their tumor was an infiltrating ductal carcinoma ⩽3 cm in diameter, surgical margins were clear by at least 2 mm, the tumor did not contain an extensive intraductal component, the axilla was surgically staged with ⩽3 nodes involved with cancer, and a postoperative mammogram was performed. Implants were positioned using a template guide delivering 50 Gy over 96 hr to the lumpectomy bed plus a 1–2-cm margin. Local control, cosmetic outcome, and complications were assessed.

Results: Patients ranged in age from 40 to 84 years (median, 65). The median tumor size was 10 mm (range, 1–25). Seventeen of 50 patients (34%) had well-differentiated tumors, 22 (44%) had moderately differentiated tumors, and in 11 (22%) the tumor was poorly differentiated. Forty-five patients (90%) were node-negative while five (10%) had 1–3 positive nodes. A total of 23 (46%) patients were placed on tamoxifen and 3 (6%) received adjuvant systemic chemotherapy. No patient was lost to follow-up. The median follow-up for surviving patients is 47 months (range, 37–59). No patient has experienced a local, regional, or distant failure. Three patients have died at 19, 33, and 39 months after treatment. All were without clinical evidence of recurrent disease and all deaths were unrelated to treatment. Good-to-excellent cosmetic results have been observed in 49 of 50 patients (98%) (median cosmetic follow-up was 44 months with a range of 19–59). No patient has experienced significant sequelae related to their implant.

Conclusions: Interim results with treatment of the tumor bed alone with an LDR interstitial implant appear promising. Long-term follow-up of

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these patients and additional studies will be necessary to establish the equivalence of this treatment approach compared to standard BCT.

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KEY WORDS: brachytherapy; breast conserving therapy

INTRODUCTION

The efficacy of breast conserving therapy (BCT) has been established in six prospective randomized trials [1–7] as well as multiple retrospective studies performed in both the United States and Europe [8–12]. Despite the equivalence of this treatment approach compared to traditional mastectomy, only 10%–40% of patients who are potential candidates for BCT actually receive it [13–18]. The factors responsible for the underutilization of BCT are multifactorial relating in part to both physician preference and patient convenience [14–18]. In addition, since standard BCT generally requires 5 to 7 weeks of daily radiation treatments to complete, logistical problems can prove prohibitive, particularly for elderly patients or those living significant distances from treatment facilities [17]. Since a substantial number of patients also require adjuvant chemotherapy [19], integrating local and systemic therapies can also present an additional barrier to the widespread use of breast conserving techniques [20].

In an effort to improve the accessibility, convenience, and logistics of BCT, we initiated a pilot trial to test the technical feasibility and acute toxicity of interstitial brachytherapy directed only to the tumor bed after lumpectomy in selected patents with early-stage breast cancer treated with BCT. Our preliminary findings revealed that the technique was well tolerated and reproducible with minimal acute toxicity [21]. This report presents the clinical outcome of the first 50 patients treated on this protocol after a median follow-up of 47 months.

MATERIALS AND METHODS

Between 1 March 1993 and 12 January 1998, 91 patients with stage I and II breast cancer were entered into a pilot trial testing the technical feasibility and acute toxicity of low-dose-rate (LDR) brachytherapy of the tumor bed alone after lumpectomy as part of their breast conserving therapy. In order to evaluate interim cosmetic results and toxicity with sufficient follow-up, only patients with a minimum follow-up of 36 months were included in this analysis. The study population thus consisted of 50 patients.

A complete listing of the eligibility criteria for enrollment into the protocol has been previously reported [21]. Briefly, patients were eligible if they met all of the following criteria: (1) the primary tumor was an infiltrating ductal carcinoma (IDC) $\leqslant$3 cm in maximum dimension; (2) margins of the lumpectomy specimen were inked and a tumor free space $\geqslant$2 mm was obtained; (3) a limited axillary dissection (levels I and II) was performed with $\leqslant$3 lymph nodes involved with cancer (no extracapsular extension); (4) pre- and postoperative mammograms were performed in order to exclude residual microcalcifications in the breast; (5) there was no evidence of an extensive intraductal component (EIC) in the primary tumor; (6) the breast was technically suitable for an interstitial implant; (7) the implant could be performed within 8 weeks of the last breast surgery; and (8) patients were $\geqslant$40 years of age. Conditions for ineligibility included: (1) patients with infiltrating lobular histology; (2) patients with diffuse, suspicious mammographic microcalcifications extending over an area greater than 3 cm in the breast or involving more than one quadrant of the breast; (3) patients with significant areas of lobular carcinoma in situ; (4) patients with pure ductal carcinoma in situ; and (5) patients with skin involvement.

Surgery

All patients underwent at least an excisional biopsy defined as a gross total resection of the primary tumor. Pathologic specimens were inked and oriented by the pathologist to define margins. In order to be enrolled in the protocol, patients with tumor free margins <2 mm underwent reexcision (at a separate surgical procedure) until adequate margins ($\geqslant$2 mm) were obtained. Patients who did not undergo perioperative implants generally had the lumpectomy cavity clipped by the surgeon to define the target volume to be implanted. In these cases, clips were placed at the superior, inferior, medial, lateral, anterior, and posterior borders of the cavity. All patients underwent axillary dissection confined to levels I and II of the axilla.

Implant Technique

All patients were treated with an LDR interstitial implant with iodine 125 (I-125). Implants were placed either perioperatively, e.g., at the time of re-excision, or postoperatively, within 8 weeks of the last breast surgery. The target volume was defined as that volume encompassed by an irregularly shaped surface approximately 1–2 cm outside of the excision cavity as defined intraoperatively or with the use of surgical clips, ultrasonography, or computed tomography (CT).

Our implant technique has been previously reported [21]. Implants placed at the time of reexcision were per-

TABLE I. Patient and Tumor Characteristics

Characteristic		Number	%
Age at diagnosis (years)	40–60	18	36
	61–70	15	30
	>70	17	34
Menopausal status	Premenopausal	4	8
	Postmenopausal	46	92
Tumor grade	Well differentiated	17	34
	Moderately differentiated	22	44
	Poorly differentiated	11	22
Nodal status	Negative	45	90
	Positive	5	10
Estrogen receptor status	Positive	39	78
	Negative	6	12
	Not performed/quantity not sufficient	5	10
Final margins (mm)	⩾2, <5	14	28
	⩾5, <10	3	6
	⩾10	33	66

formed with the assistance of the treating surgeon. All implants were performed in the operative suite using local or general anesthesia. For closed cavity implants, patients underwent preimplant ultrasonography and the boundaries and dimensions of the lumpectomy cavity were recorded and marked on the skin surface [22]. If clips were placed at the time of lumpectomy, a preimplant simulation was performed and the position of these clips was projected on the skin surface to outline the biopsy cavity [23]. If the lumpectomy cavity could not be adequately identified, patients were not considered technically suitable for enrollment into the protocol.

Implants were constructed using a template guide with fixed needle positions. Intercatheter separation on the template was fixed at 15 mm and the interplane separation was 14 mm. Templates of two or three planes were available depending on the size of the breast and biopsy cavity. Implant needles were positioned at the boundaries of the target volume. Intraoperative ultrasound was used to verify accurate needle placement if the implant was placed with a closed lumpectomy cavity. After implant needles were positioned, they were replaced with hollow plastic afterloading tubes. A simulation was performed for dosimetric evaluation and to confirm adequate coverage of the target volume (e.g., surgical clips within the boundaries of the target volume on radiographs or a CT scan documenting accurate placement of catheters). If adequate dosimetric coverage of the target volume could not be verified (or if all pathologic eligibility criteria were not met), the patient was not considered a candidate for the protocol and the implant was either used to deliver a boost of 1,600 cGy prior to whole breast irradiation or it would be removed.

Radiation

A minimum dose of 5,000 cGy (encompassing the desired target volume) at 52 cGy/hr was delivered in all patients. Strict homogeneity criteria (previously outlined) were employed in all patients [21]. Patients received their treatment in a private hospital room. After 96 hr, seeds and catheters were removed at the beside and patients were discharged home.

Follow-Up

Patients were seen in follow-up at 3–6-month intervals by either their radiation oncologist or surgeon. Mammograms were obtained 6 months after the completion of brachytherapy and then yearly. Cosmetic results were evaluated by the treating radiation oncologist using the system developed by the Harvard Group [12]. Acute toxicities were scored using the Radiation Therapy Oncology Group (RTOG) acute radiation morbidity scoring criteria and late toxicities were evaluated using the RTOG/European Organization for the Research and Treatment of Cancer (EORTC) late radiation morbidity scoring scheme for skin and subcutaneous tissue. Implant quality was judged using criteria established by Wu et al. [24]. The homogeneity index (HI) was calculated for each patient as the fraction of the implant volume encompassed by the 100% isodose line, which received less than 1.5 times the prescribed dose. Implant quality was judged as fair if the HI was >0.4 and ⩽0.5, good with values >0.5 and ⩽0.7 and excellent with a HI > 0.7 [21]. All intervals were calculated from the completion of brachytherapy. Follow-up was complete through 28 February 1998.

RESULTS

Patient and tumor characteristics are listed in Table I. The median age at diagnosis was 65 years (range, 40–84). The median tumor size was 10 mm (range, 1–25). In 15 patients (30%), the interstitial implant was placed at the time of reexcision/axillary dissection with an open cavity. In 35 patients (70%), the implant was placed with

a closed cavity either at the time of axillary dissection in 6 (12%) or at a separate procedure in 29 (58%) patients.

Adequate target volume coverage was verified radiographically in all patients. No patient required premature implant removal, nor was it necessary to use the implant to deliver only a boost. Implant quality was calculated as good in 14 patients (HI > 0.5) and excellent in 36 (HI > 0.7). The median HI was 0.77 with a range of 0.59 to 0.83.

A total of 23 patients (46%) were placed on adjuvant tamoxifen after brachytherapy was completed. Three additional patients (6%) also received adjuvant systemic chemotherapy beginning 2 to 3 weeks after their interstitial implant.

The median follow-up for surviving patients was 47 months (range, 37–59). No patient has experienced a local, regional, or distant failure. Three patients died at 19, 33, and 39 months after their diagnosis. All were clinically free of recurrent disease at the time and all deaths were unrelated to treatment. The other 47 patients are all alive with no evidence of disease (NED). In the total group of 91 patients, the median follow-up was 36 months. No patient has experienced a local, regional, or distant failure.

A total of 41 patients (82%) experienced acute skin reactions (RTOG grade 1) in close proximity to the needle puncture sites. No RTOG grade 2, 3, or 4 acute skin reactions were noted. Only one grade 2 RTOG/EORTC late skin or subcutaneous tissue toxicity was noted (moderate skin telangiectasia in implanted tumor bed). All other late reactions were either grade 0 or 1. Good-to-excellent cosmetic results have been observed in 49 of 50 (98%) patients (median cosmetic follow-up time was 44 months with a range of 19–59 months). A total of nine patients (18%) developed small (<2 mm) areas of telangiectasia at 1–3 needle puncture sites. No patient has experienced significant sequelae related to their implant.

DISCUSSION

In the current analysis, we reviewed the clinical outcome of treating the tumor bed alone with LDR interstitial brachytherapy in a series of 50 consecutive patients with early-stage breast cancer treated with BCT. With a median follow-up of 47 months (minimum follow-up of 37 months), no patient experienced a local, regional, or distant failure. In addition, cosmetic results were judged to be good to excellent in 49 (98%) patients and no RTOG grade 2, 3, or 4 acute skin toxicities were noted. These interim data suggest that irradiation directed to the lumpectomy cavity alone may ultimately prove efficacious and offer selected women with early-stage breast cancer an additional treatment alternative in the management of their malignancy.

Although BCT has consistently been shown to produce equivalent survival results to mastectomy, only 10%–40% of patients who are candidates for this approach actually receive it [13–16]. The factors responsible for the underutilization of breast conservation are multiple, primarily reflecting the issues of convenience, limited transportation, normal tissue toxicity, and a prolonged time commitment (14). By delivering irradiation in only 4 days shortly after lumpectomy, we have attempted to eliminate many of the logistical problems associated with BCT that may have an impact on a woman's decision not to conserve her breast. In addition, the issue of integrating systemic chemotherapy with irradiation is avoided since all aspects of breast conservation are completed within a very short period of time.

TABLE II. Incidence of Elsewhere Failures Versus Treatment Technique (Crude Rate)

Trial [Reference No.]	Follow-up (months)	Surgery alone		Surgery plus irradiation	
		Number	%	Number	%
NSABP-B06 [5]	144	17/636	2.7	24/629	3.8
Milan III [38]	39	4/273	1.5	0/294	0
Ontario [27]	91	15/421	3.6	4/416	1
Uppsala-Orebro [33]	65	7[a]/187	3.7		

[a]Estimated from report.

The scientific rationale for irradiating the tumor bed alone after lumpectomy is based on a review of several trials that have explored the outcome of treating early-stage breast cancer patients with either lumpectomy alone or followed by whole-breast irradiation [5,25–38]. In the randomized studies reported in Table II, the vast majority of recurrences that developed in patients who did not receive whole-breast radiation therapy were in the tumor bed [5,27,33,38]. The incidence of failures outside of the lumpectomy cavity was extremely low and did not appear to be significantly affected by the use of whole-breast radiation therapy. This suggests that radiation therapy after lumpectomy exerts its primary effect on occult microscopic disease in the tumor bed. In addition, studies of BCT with long-term follow-up (Table III) also suggest that the incidence of recurrences in the breast outside of the boost volume (e.g., elsewhere failures) is not significantly different than in patients who do not receive radiation after lumpectomy [7–10,38,39]. Collectively, these data imply that in certain patients, whole-breast radiotherapy may not be required and that lumpectomy bed irradiation alone may provide an acceptable outcome.

Several other investigators have also explored brachytherapy as the sole radiation modality after lumpectomy [40–46]. Both LDR and high-dose-rate (HDR) techniques have been performed (Table IV). One of the trials using LDR brachytherapy with the longest follow-up is from Guys Hospital in London [41,42]. Twenty-seven

TABLE III. Incidence of Elsewhere Failures After Standard Breast Conserving Therapy (Crude Rates)

Series [Reference No.]	Follow-up (months)	Number of patients	%
William Beaumont Hospital [39]	118	13/400	3.3
University of Pennsylvania [9]	70	17/1,030	1.7
Marseille [11]		38/1,593	2.4
Institut Curie [8]	103	30/518	5.8
Milan [38]	39	19/1,232	1.5
NSABP-B06 [5]	144	24/629	3.8
Joint Center for Radiation Therapy [10]	116	27/974	2.8

TABLE IV. Irradiation of the Tumor Bed Alone

Institution [Reference no.]	Follow-up (months)	Number of patients	Dose, cGy	Total dose, cGy	% local recurrence	Cosmetic results (%) good/excellent
High-dose-rate series						
Ochsner Clinic [43]	50	36	400 × 8	3200	0	67
Royal Devon/	18	45	1000 × 2	2000	8.8	95
Exeter Hospital,			700 × 4	2800		
Exeter England [40]			600 × 6	3600		
London Regional Cancer Center,						
London, Ontario [44]	20	39	372 × 10	3720	2.6[a]	>95
William Beaumont Hospital [45]	14	17	400 × 8	3200	0	
Low-dose-rate series						
William Beaumont Hospital [21]	20	60	52 cGy/hr	5000	0	100
Guys Hospital [41,42]	72	34	40 cGy/hr	5500	37[a]	83
Ochsner Clinic [43]	50	26		4500	0	78
Cionini et al. [46]	27	90		5840	4.4[a]	
External beam series						
Christie Hospital [46]	37	353	531	4250	13[b]	

[a]Crude rate.
[b]Five-year actuarial rate.

patients were treated with an LDR interstitial implant using a rigid template. The lumpectomy bed plus a 2-cm margin was implanted with iridium wire delivering 55 Gy over 5.5 days to 85% of the basal dose rate as defined by the Paris System. With a median follow-up of 6 years, 10 patients (37%) developed an isolated recurrence in the breast. No serious side effects in normal tissues were seen. Unfortunately, this trial was severely limited by the surgical techniques utilized. No attempt was made to achieve wide excision either grossly or microscopically. This study emphasizes that patients who are not optimal candidates for breast conserving therapy should clearly not be treated with brachytherapy alone. Interestingly, only 1 of 10 failures in the breast was outside of the irradiated volume, suggesting that elective irradiation of the whole breast may not be required in certain selected patients.

External beam radiotherapy directed only to the tumor bed has also been explored (Table IV). Ribeiro et al. [47] reported on a study at the Christie Hospital and Holt Radium Institute of 708 patients treated for breast cancer. Patients were randomized to receive either quadrant irradiation (usually 10-MeV electrons, average field 6 × 8 cm, 42.5 Gy in 8 fractions) or tangential whole-breast irradiation with 4-MV photons (40 Gy in 15 fractions). The 5-year actuarial recurrence rate in the breast was 6% in the whole-breast irradiation group and 13% in the local-field-treated patients. Patients with infiltrating lobular carcinoma had a 20% recurrence rate in the local field group. Ten patients in the local field and two in the breast irradiation group developed fat necrosis. It should be noted that not all patients in this study had gross tumor excision and that ultrasonography or CT scans were not used to guide radiation treatment. In addition, selection criteria were much less stringent than in the present study.

In the current protocol, the target volume was designed to irradiate at least 1–2 cm of breast tissue beyond the lumpectomy cavity in all dimensions if technically possible. This margin was based on data by Holland et al. [48] that show that residual cancer cells can extend 2 cm beyond the edge of a tumor after simulated gross excision in 29% of patients without an EIC. Though radiographic verification of adequate target volume coverage by implant catheters was required in all patients, additional dosimetric techniques (three dimensional dose/volume

TABLE V. Local Recurrence Rate After Tumor Excision Alone or Followed by Whole-Breast Irradiation

Author [Reference no.]	Follow-up (months)	Tumor size (cm)	Surgery	Local recurrence rate[a]	
				Surgery alone	Surgery plus radiation therapy
Cedermark et al. [25]	6–60	≤2	Partial mastectomy	15.5% (58)	2.9% (204)
Clark et al. [21]	312	≤5	Local excision	29% (374)[b]	14% (1130)[b]
Clark et al. [27]	91	≤4	Lumpectomy and axillary dissection	35% (421)	11% (416)
Cooke et al. [28]	39	Not given	Partial mastectomy	21% (53)	5% (44)[c]
Fisher et al. [2]	81	≤4	Partial mastectomy		
			−Axillary nodes	37% (361)[c]	12% (377)[c]
			+Axillary nodes	43% (211)[c]	6% (192)[c]
Forrest et al. [29]	68	≤4	Local excision and axillary dissection	24.5% (294)	5.8% (291)
Kantorowitz et al. [30]	52	≤5	Local excision	28.6% (77)	14.2% (106)
			Quadrantectomy	22.2% (18)	2.8% (36)
Liljegren et al. [33] Uppsala-Orebro Breast Study Group	65	≤2	Sector excision and axillary dissection	18.4% (197)[c]	2.3% (184)[c]
Whelan et al. [31]	66	≤4	Lumpectomy and axillary dissection	30% (396)[d]	8% (403)
Veronesi et al. [38]	39	≤2.5	Quadrantectomy	8.8% (273)	0.3% (294)

[a]Patient numbers in parentheses.
[b]Ten-year actuarial relapse rate.
[c]Eight-year actuarial relapse rate.
[d]Five-year actuarial rate.

analyses) will be needed in future studies to correlate tumor control probability with lumpectomy cavity coverage and dose.

Part of the concern with the use of brachytherapy to treat breast cancer has been the belief that reproducibility and accuracy are operator-dependent and, therefore, quality control cannot be ensured from patient to patient. However, by performing the implant with a customized template and by employing very strict brachytherapy guidelines (e.g., defined homogeneity criteria and source position relative to the skin) many of these concerns can be eliminated. For example, implant quality as judged by the homogeneity index was found to be excellent in 35 (70%) patients treated with the current protocol and good in all others. In addition, if the implant is performed at the time of lumpectomy, visual verification of adequate target volume coverage can be immediately obtained. The recently opened phase I/II RTOG 95-17 trial employing brachytherapy alone in selected patients with breast cancer was developed with many of the above concerns in mind. Patients cannot be enrolled in this trial if (1) adequate postimplant target volume coverage cannot be verified; (2) strict dosimetric criteria are not met; and (3) all pathologic requirements are not fulfilled. This well-designed clinical trial should clearly address many of these issues and accurately evaluate the efficacy of this treatment approach.

If brachytherapy alone does prove efficacious, it will provide an additional treatment alternative for selected low-risk breast cancer patients that is intermediate between observation alone (after excisional biopsy) and full-breast irradiation. There have been multiple trials attempting to identify subsets of patients who may do well without radiation therapy following excisional biopsy alone (Table V). However, no consistent subgroup of patients has been identified that has achieved a high enough rate of tumor control to justify the elimination of all radiation therapy [2,25–31,33–35,38,49–52]. Brachytherapy alone may offer these selected low-risk patients a higher probability of tumor control without the logistical problems associated with conventional techniques of radiation therapy.

CONCLUSION

Interim results with irradiation directed only to the tumor bed using interstitial LDR brachytherapy appear promising. Local tumor control, acute and chronic toxicity, and cosmetic results have been comparable to conventional BCT with a median follow-up of 47 months. However, longer follow-up and additional studies will be required to establish the efficacy of this treatment approach and the patients most suitable for its application.

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